

CLAIMS

What is claimed is:

1. A transgenic mouse characterized by a reduced heart rate having incorporated into its genome a transgene comprising a nucleic acid encoding a mouse cardiac alpha myosin heavy chain including a modification which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of said cardiac alpha myosin heavy chain thereby reducing an ADP dissociation rate of said mouse cardiac alpha myosin heavy chain wherein said mouse cardiac alpha myosin heavy chain exhibits: (a) reduced contractility (speed of contraction); and (b) increased power generating capability (work capacity) resulting in the transgenic mouse exhibiting a reduced heart rate.
2. A transgenic mouse according to claim 1 wherein said modification comprises an S342G mutation in said loop 1.
3. A transgenic mouse according to claim 1 wherein said modification comprises a substitution of loop 1 of mouse cardiac alpha myosin heavy chain by a non-mouse myosin heavy chain loop 1 (ATPase loop).
4. A transgenic mouse according to claim 3 wherein said non-mouse myosin heavy chain loop 1 is a rat, pig or human beta myosin heavy chain loop 1 (ATPase loop).
5. A transgenic mouse according to claim 1 wherein said modification comprises a substitution of said interactive micro-domain of mouse cardiac alpha myosin heavy chain by a non-mouse myosin heavy chain interactive micro-domain.

6. A method for studying molecular and cellular aspects associated with a transgenic mouse having a reduced heart rate, comprising the steps of:

(a) harvesting cells, tissues or both from a transgenic mouse according to claim 1; and

5 (b) examining the cells, tissue or both from the transgenic mouse to determine if

they differ in one or more molecular or cellular aspects from cells and tissues harvested from a transgene-negative mouse in order to identify molecular or cellular aspects associated with said transgenic mouse having a reduced heart rate.

10 7. A method of identifying compounds useful for treating or preventing cardiac disease, comprising the steps of:

(a) providing a first transgenic mouse and a second transgenic mouse, both according to claim 1;

(b) administering a compound to be evaluated to the first transgenic mouse;

15 and

(c) evaluating physiological and pathological changes in the first transgenic mouse compared to the second transgenic mouse that did not receive the compound to determine the efficacy of the compound in treating or preventing cardiac disease.

8. A method for evaluating the effects of external factors selected from the group consisting of diet, exercise and combinations thereof on cardiac disease, comprising the steps of:

(a) establishing a normal control regimen for an external factor in a first transgenic mouse and a second transgenic mouse, both according to claim 1;

- (b) modulating the regimen for the external factor in the second transgenic mouse; and
- (c) monitoring the second transgenic mouse for a difference in a characteristic associated with cardiac disease compared to the first transgenic mouse.

5 9. A recombinant nucleic acid molecule comprising a nucleic acid sequence encoding an amino acid sequence of a mouse cardiac alpha myosin heavy chain, said nucleic acid sequence having a mutation comprising a modification which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of said cardiac alpha myosin heavy chain thereby reducing an ADP dissociation rate of said mouse cardiac alpha 10 myosin heavy chain wherein said nucleic acid sequence is operatively linked to one or more expression control sequences.

10. A recombinant nucleic acid molecule according to claim 9 wherein said modification comprises an S342G mutation in said loop 1.

11. A recombinant nucleic acid molecule according to claim 9 wherein said 15 modification comprises a substitution of loop 1 of mouse cardiac alpha myosin heavy chain by a non-mouse myosin heavy chain loop 1 (ATPase loop).

12. A recombinant nucleic acid molecule according to claim 11 wherein said non-mouse myosin heavy chain loop 1 is a rat, pig or human beta myosin heavy chain loop 1 (ATPase loop).

20 13. A recombinant nucleic acid molecule according to claim 9 wherein said modification comprises a substitution of said interactive micro-domain of mouse cardiac alpha myosin heavy chain by a non-mouse myosin heavy chain interactive micro-domain.

14. A method for producing a transgenic mouse characterized by a reduced heart rate according to claim 1, comprising steps of:

- (a) introducing into an embryonal cell of a mouse a recombinant nucleic acid molecule according to claim 9;
- 5 (b) transplanting the transgenic embryonal target cell formed thereby into a recipient female parent; and
- (c) identifying at least one transgenic offspring containing said recombinant nucleic acid molecule in said offspring's genome, wherein said offspring: (i) expresses said recombinant nucleic acid molecule in its cardiac tissue; and (ii) displays a reduced heart rate as 10 compared to a negative transgenic offspring mouse.